Statistical analysis plan (SAP) for:

One-year clinical course of back-related disability and prognostic value of comorbidity on disability during one year follow-up in older patients visiting primary care with a new episode of back pain

Project:

BACk pain in Elders in Norway (BACE-N): a prospective cohort study of older people visiting primary care with a new episode of back pain

NCT identifier: NCT04261309
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Administrative information

Scope

This document is a supplement to the BACE-N protocol (ClinicalTrials.gov Identifier: NCT04261309) The current Statistical Analysis Plan has been written while data collection was ongoing (we had access to baseline data, but not to follow-up data) and it will be uploaded to the ClinicalTrials.gov before full access to the study database.

Working title

One-year clinical course of back-related disability and prognostic value of comorbidity on disability during one year follow-up in older patients visiting primary care with a new episode of back pain

Version of SAP

1.0

Ethical approval

The BACE-N study was deemed a "quality control project" by the Regional Ethical committee, and treatment by the ethical committee was thus not considered necessary as per 11.11.2014 (reference number: 2014/1634/REK vest)

Approval from the Norwegian Social Science Data Service was obtained on 02.03.2015 (reference number: 42149).

Names, affiliations and roles of SAP contributors

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Study sponsor

The BACE-N-study has received funding from Oslo Metropolitan University, The Norwegian Fund for Post-Graduate Training in Physiotherapy and “Et liv i bevegelse” (A life in movement) – Norwegian chiropractors’ research foundation.

Signatures

_____	_____	_____
Ørjan Nesse Vigdal	Milada C. Småstuen	Margreth Grotle
Main author of SAP	Statistical advisor	Principal investigator

Introduction

Background and rationale for study

Back pain is common in all age groups (1), and one systematic review highlights that disabling back pain is more prevalent in older people than in younger people (2). The clinical course of back-related disability in older adults with back pain has not been extensively studied. Two studies suggests that improvements in disability were modest the first three months, with little to no improvements on group level after three months (3, 4). It is well documented that number of comorbidities are associated with the clinical course of back-related disability in older adults, but the prognostic value of comorbidity is still highly uncertain (5-11).

Study aim:

The primary aim of this study is to examine the clinical course of back-related disability measured at baseline, 3, 6 and 12 months after a new episode of back pain. The secondary aim is to assess the prognostic value of number and severity of comorbidity at baseline for changes in back-related disability over one year of follow-up.

Study design and method

Study design

BACE-N is based on the previously published BACE study protocol from the BACE international consortium (12). The BACE-N protocol has been published (ClinicalTrials.gov Identifier: NCT04261309).

The BACE-N study is a prospective observational cohort study with a 2-year follow-up time. This study will use data from baseline, 3, 6 and 12 months of follow-up. Design of the study was made within the framework PROGnosis RESearch Strategy (PROGRESS), which is a framework for ensuring and enhancing the quality of prognostic studies (13). The primary aim is relating overall prognosis, and the secondary aim is relating confirmatory prognostic factor research (13, 14).

Study population

Patients aged ≥55 years visiting a general practitioner (GP), physiotherapist or chiropractor for a new episode of back pain are invited to participate in the study. Back pain is defined as pain located in the region from the top of the scapula to the sacrum, with or without radiating leg pain. An episode of back pain is defined as “new” if the patient has not received health care for the same back complaint during the last 6 months. The exclusion criteria were: Difficulty completing the study questionnaires due to language or cognitive difficulties, mobility impairments impeding the clinical examination (wheelchair-bound patients), had received healthcare for the same back complaint during the last 6 months (notwithstanding care initiated within the previous 4 weeks from time of baseline assessment).

Data collection

At baseline, patients receive a clinical examination and questionnaire. Patients are then given a follow-up questionnaire either through email or mail at 3-months, 6-months and 12-months follow-up.

Description of treatment received during follow-up

The study participants continue their health care in agreement with their healthcare provider regardless of inclusion in the study. This means that patients may receive education and advice, exercise therapy, massage, manipulations, mobilizations, pharmacological therapy, or additional diagnostic testing and referrals, all of which constitutes "usual" primary care (15). Treatment given is at the discretion of the healthcare provider and the patient.

Variables

Outcome measure:

Back-related disability, measured using the Norwegian, validated version of the Roland-Morris Disability Questionnaire (RMDQ) (16, 17). This is a questionnaire with 24 statements regarding abilities to perform ADL tasks, with a dichotomous yes/no answer. The answers are summed to a total score ranging from 0-24, where 0 indicates no disability and 24 indicates "maximum" disability. RMDQ has been found to measure several dimensions of back-related disability (18). We plan to use RMDQ as a continuous measure, as recommended by the PROGRESS framework (14). This will ensure easier comparability to similar studies, and easier inclusion in future meta-analyses.

RMDQ is measured at baseline, 3 months, 6 months and 12 months.

Prognostic factor measurement:

The prognostic factor of interest is comorbidity measured at baseline with a modified version of the Self-administered Comorbidity Questionnaire (SCQ) (19). The original questionnaire measures 13 pre-specified comorbidities, and 2 non-specified. The item "back pain" has been removed for this study and replaced with an additional non-specified item. Thus, the count of comorbidity ranges from 0-15. The diseases listed are: Heart disease, high blood pressure, lung disease, diabetes, ulcer or stomach disease, kidney disease, liver disease, anemia or other blood disease, cancer, depression, osteoarthritis, rheumatoid arthritis and up to 3 non-specified comorbidities. The SCQ measures comorbidities on three levels: 1) Do you have the problem? 2) Do you receive treatment for it? 3) Does it limit your activities? All levels are answered on a dichotomous yes/no level, and you only answer level 2 and 3 if you have answered "yes" on level 1. An individual can receive a maximum of 3 points for each medical condition: 1 point for the presence of a comorbidity, 1 point if they receive treatment for the condition, and 1 point if the condition limits their functioning. The maximum score for the full SCQ is thus 45 points.

We plan to use SCQ part 1 comorbidity count (0-15 scale), and the full SCQ (0-45) in separate models. Previous studies have found linear relationships between comorbidity and back-related disability (7, 11), and thus we plan to treat these variables as linear. Linearity with outcome will be assessed, and deviations will be handled appropriately.

Covariates:
Covariates are presented in table 1. They are chosen based on being "established" prognostic factors in the literature, having been utilized in similar studies previously (to enhance comparability), and for being readily available and easy to measure in clinical practice.

Table 1: Covariates, measurement level and/or instrument, rationale for inclusion

Factor	Measurement level	Rationale
Age	Continuous, minimum age ≥55	Standard covariate in previous studies (7, 8, 10), and in some studies reported to be associated with disability levels in older adults (4, 6, 20)
Sex	Dichotomous	Standard covariate in previous studies (7, 8, 10), and in some studies reported to be associated with disability levels in older adults (6, 20)
BMI	Measured continuous, divided into categories: <20, 20-25, 25-30, <35	Covariate in previous study (7), and found to be associated with disability in older adults (4, 21)
Back pain duration	Measured in days, but categorized to an ordinal scale of 3 categories: 0-6 weeks, 6-12 weeks, >12 weeks, similar to other BACE studies (22)	Covariate in previous study (8), and found to be associated with disability in older adults (4, 6, 11, 20)
Baseline disability	Continuous. Roland-Morris disability questionnaire, 0-24 scale.	Standard covariate, given the outcome is disability. Only applicable if not using mixed models.
Pain severity last week	Continuous. Numeric rating scale 0-10.	Associated with disability in one study in older adults (4).
Expectation of recovery within the next three months	5-point ordinal Likert scale. From "I am fully recovered" to "I am worse than ever".	Consistently associated with disability in older adults (4, 6, 11)

Statistical power consideration

The published protocol for the BACE-N study estimates that we need a total of 450 patients included in the study. Allowing a 15% dropout rate at 12 months, we will have approximately 380 participants available at 12 months.

We used the power estimation tool in Stata to determine level of statistical power. With a sample size of 450, and an estimated r^2 of 0.30 for the full model of comorbidity adjusted for covariates, we have over 90% power to detect an r^2-change of 0.017 or higher when adding comorbidity to the model.

Handling of missing data

Missing data will be handled with multiple imputation, using 5 imputations and 10 iterations unless the missing exceeds 30% and missing at random cannot be assumed. We will use the fully conditioned specification method, and regression estimation. For variables where we are unable to use regression estimation due to computational difficulties, predictive mean matching will be used (23).

Missing values for RMDQ will be handled by replacing missing items with the mean of the answered items for the individual, if less than 30% of the items are missing.

A mixed model, which we intend to use for the primary and secondary aim, does not require variable level imputation for the outcome measure. However, missing values on item level on

the RMDQ might still be an issue. To solve this, we will replace missing items for RMDQ with the mean of the answered items for the individual, if less than 7 (30%) of the 24 items are missing.

Statistical analyses

General statistical considerations

Analyses described in this statistical analysis plan are considered a priori analyses. Possible post-hoc exploratory analyses will be explicitly identified in the article. All analyses will be carried out by the first author using Stata version 16, under supervision from the principal investigator and the advisory statistician. The statistical tests will be 2-sided, and p-value will be reported. If the p-value is less than 0.05, the test is deemed statistically significant. 95% confidence intervals will be reported on point estimates.

Statistical analyses

Description of study flow and study sample:

The flow of participants will be reported with a flow chart. Reasons for exclusion and loss to follow-up will be provided where known. Descriptive data of the study sample will be reported using mean and standard deviation for normally distributed continuous variables, median and interquartile range for variables with skewed distrubution, and with frequency and proportions for categorical variables. Normal distribution will be examined visually using histogram and QQ-plot, and statistically with the Kolmogorov-Smirnov test. Baseline characteristics will be presented in a table. See proposed tables and figures below.

Descriptive statistics will be used to present the mean and standard deviation if RMDQ is normally distributed, or median and interquartile range if RMDQ is not normally distributed, for each time point: Baseline, 3 months, 6 months, 12 months. This will also be presented graphically, similarly to van der Gaag et al (3). This graphical presentation will also be performed stratified for number of comorbidities.

A person may be a responder at one time-point and a non-responder at another. Therefore, an analysis of responders versus non-responders will be performed for each time point, using bivariate analysis for baseline characteristics (chi square test, Individual Samples T-test, or Mann Whitney U-test). Results from these analyses will be presented in text, and the table available in supplementary material.

Model choice and model building strategy:

According to the STRATOS initiative task force, a complete prespecifying of all aspects in model building is unrealistic in observational studies (24). Thus, the following will provide a framework for analysis and model building in this study, not a detailed recipe. Decisions regarding final choice of models will be made by the first author, the advisory statistician and the principal investigator.

Primary aim, clinical course of back-related disability:
Mixed models for repeated measures will be used to account for statistical dependencies. RMDQ is the dependent variable, and time and first contact health provider will be entered as fixed factors. The exact handling of time as a continuous or categorical variable depends on the distribution. Previous studies have found that the clinical course of a back episode is not linear over time (3, 25, 26). It is therefore reasonable to believe that time will have to be treated as a categorical variable, or by introducing a quadratic term, depending on its distribution. Choice of covariance matrix is dependent on data structure. Interaction between first contact health provider and time will be analysed.

Secondary aim, prognostic value of number and severity of comorbidities on the course of back-related disability:
We will fit separate models for count of comorbidity (SCQ part 1, 0-15 scale) and count and severity of comorbidity (full SCQ, 0-45). The steps are outlined below:

1. The univariate association between SCQ and RMDQ over time will be assessed with a mixed model for repeated measures. An interaction term for SCQ*time will be tested, and kept if statistically significant. We will present the crude regression estimates from this analysis.

2. A mixed model with all the covariates from Table 1 and RMDQ over time will be fitted. From this model, r^2 will be presented as a measure of prognostic value.

3. SCQ will be added to the model from step 2. The adjusted regression estimate, and the r^2-change from step 2 to step 3 will be presented.

Previous studies have found a linear relationship between number and severity of comorbidity and disability (7, 27). Linearity between SCQ and RMDQ will be assessed with a scatter-plot. In case of non-linearity between SCQ and RMDQ comorbidity count and disability score, the following alternatives will be discussed (24, 28):

- Categorization of SCQ
- Transformation (logarithmic or cubic) of SCQ
- Fractional polynomials for SCQ
- Spline functions for SCQ

Sensitivity analyses

Complete case analyses will be performed to assess possible bias introduced by the multiple imputation procedures.

Proposed tables and figures

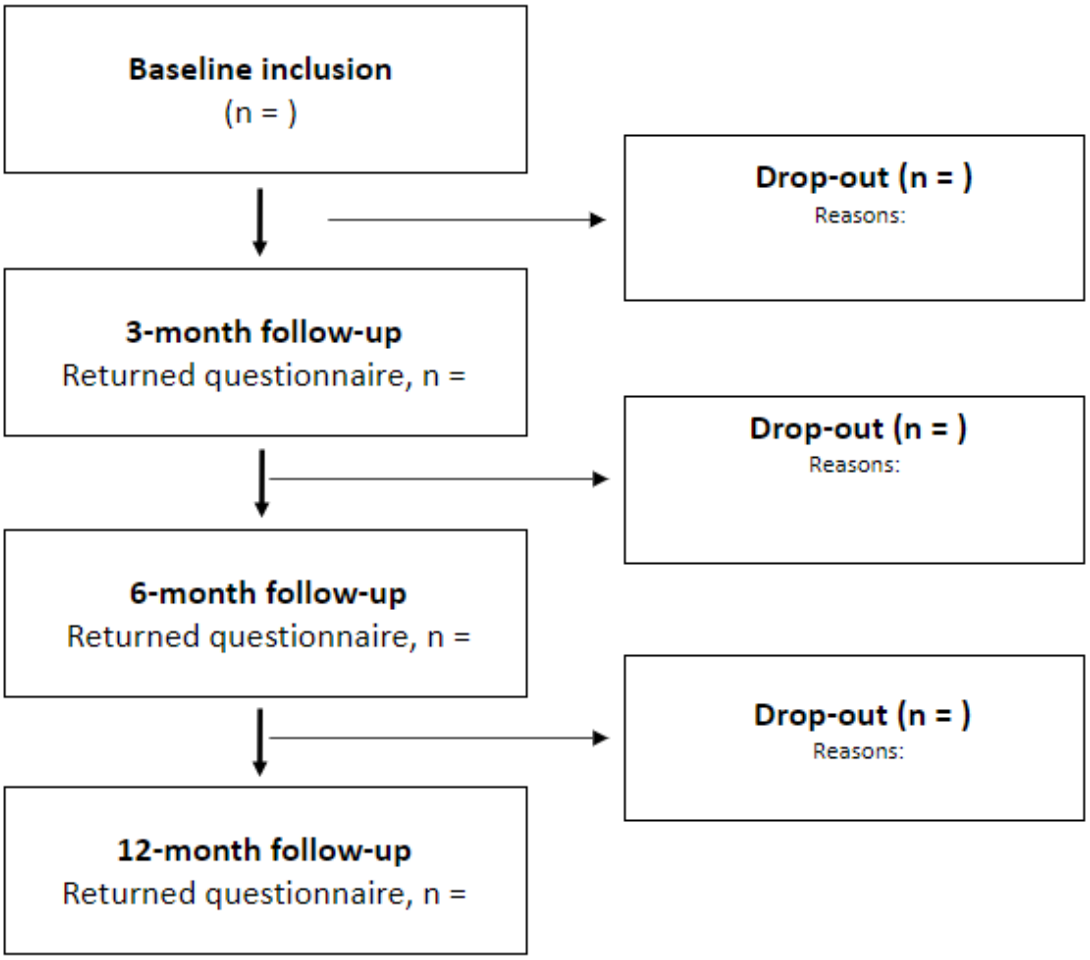


Figure: Flowchart of study participants

Baseline characteristics:

Table: Baseline characteristics

Variable	n	Values
Sociodemographic variables		
Age, median (IQR)		
Female, n (%)		
Married or living with partner, n (%)		
Education level high, n (%)		
General health variables		
Health-related quality of life (SF-36), median (range)		
Physical component score		
Mental component score		
Hazardous alcohol consumption (AUDIT-C), n (%)		
Smoking status, n (%)		
Current smoker		
Smoked previously		
Never		
Falls efficacy (FES-I), median (range)		
Back pain history and characteristics of current episode		
First healthcare provider		
General practitioner		
Physical therapist		
Chiropractor		
History of back pain, n (%)		
Using pain medication, n (%)		
Sleep problems weekly due to back pain, n (%)		
Back pain (NRS 0-10) (figure?), median (range)		
Disability (RMDQ 0-24) (figure?), median (range)		
Duration of current episode, n (%)		
0 – 6 weeks		
6 weeks – 3 months		
> 3 months		
Psychological variables		
Kinesiophobia (FABQ-PA 0-28), median (range)		
Depression (CES-D 0-60), median (range)		
Pain catastrophizing (PCS 0-52), median (range)		
Back beliefs and attitudes (BBQ 9-45), median (range)		
Expectations of back pain next 3 months (figure?), n (%)		
Fully recovered		
Much better		
No change or worse		
Psychosocial risk profile (SBT)		
Low risk		
Medium risk		
High risk		
Clinical variables		
Pain with active movements of the back, n (%)		
Positive radiculopathy diagnostic rule, n (%)		
Two or more red flags, n (%)		
Physical performance (BPS), median (range)		
Functional mobility (TUG), median (range)		

SF-36, Short Form health survey 36; AUDIT-C, alcohol use disorders identification test, score ≥3 for women and ≥4 for men ; FES-I, Falls Efficacy Scale – International; NRS, numeric rating scale; RMDQ, Roland-Morris Disability Questionnaire; FABQ-PA, Fear-Avoidance Beliefs Questionnaire – Physical Activity; CES-D, Center for Epidemiological Studies – Depression; PCS, Pain Catastrophizing Scale; BBQ, Back Beliefs Questionnaire; SBT, Start Back Tool; BPS, Back Performance Scale; TUG, Timed Up-and-Go.
*Comorbidities measured with Self-administered Comorbidity Questionnaire and a question on osteoporosis.

Appendix table: Baseline characteristics for responders vs non-responders for each time-point.

Variable	Responder 3 mo (n)	Non-responder 3 mo	Responder 6 mo (n)	Non-responder 6 mo (n)	Responder 12 mo (n=)	Non-responder 12 mo (n=)
Sociodemographic variables						
Age, median (IQR)						
Female, n (%)						
Married or living with partner, n (%)						
Education level high, n (%)						

General health variables	
Health-related quality of life (SF-36), median (range)	
Physical component score	
Mental component score	
Hazardous alcohol consumption (AUDIT-C), n (%)	
Smoking status, n (%)	
Current smoker	
Smoked previously	
Never	
Falls efficacy (FES-I), median (range)	
Back pain history and characteristics of current episode	
First healthcare provider	
General practitioner	
Physical therapist	
Chiropractor	
History of back pain, n (%)	
Using pain medication, n (%)	
Sleep problems weekly due to back pain, n (%)	
Back pain (NRS 0-10), median (range)	
Disability (RMDQ 0-24), median (range)	
Duration of current episode, n (%)	
0 – 6 weeks	
6 weeks – 3 months	
> 3 months	
Psychological variables	
Kinesiophobia (FABQ-PA 0-28), median (range)	
Depression (CES-D 0-60), median (range)	
Pain catastrophizing (PCS 0-52), median (range)	
Back beliefs and attitudes (BBQ 9-45), median (range)	
Expectations of back pain next 3 months (figure?), n (%)	
Fully recovered	
Much better	
No change or worse	
Psychosocial risk profile (SBT)	
Low risk	
Medium risk	
High risk	
Clinical variables	
Pain with active movements of the back, n (%)	
Positive radiculopathy diagnostic rule, n (%)	
Two or more red flags, n (%)	
Physical performance (BPS), median (range)	
Functional mobility (TUG), median (range)	

SF-36, Short Form health survey 36; AUDIT-C, alcohol use disorders identification test, score ≥3 for women and ≥4 for men ; FES-I, Falls Efficacy Scale – International; NRS, numeric rating scale; RMDQ, Roland-Morris Disability Questionnaire; FABQ-PA, Fear-Avoidance Beliefs Questionnaire – Physical Activity; CES-D, Center for Epidemiological Studies – Depression; PCS, Pain Catastrophizing Scale; BBQ, Back Beliefs Questionnaire; SBT, Start Back Tool; BPS, Back Performance Scale; TUG, Timed Up-and-Go.

*Comorbidities measured with Self-administered Comorbidity Questionnaire and a question on osteoporosis.

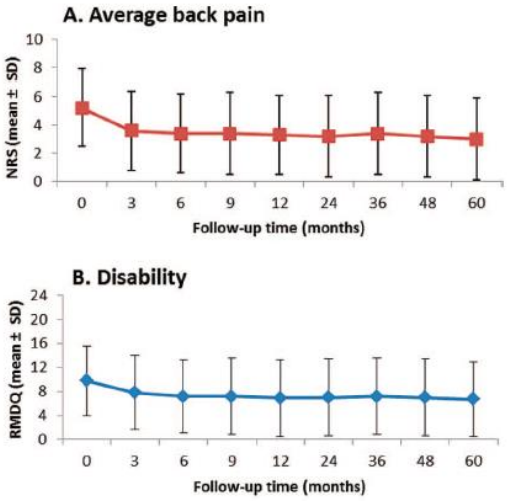
Prevalence of each comorbidity:

Table: Prevalence of each comorbidity at baseline

Comorbidity	**N**	**%**
Heart disease		
High blood pressure		
Lung disease		
Diabetes		
Ulcer or stomach disease		
Kidney disease		
Liver disease		
Anemia or other blood disease		
Cancer		
Depression		
Osteoarthritis		
Rheumatoid arthritis		
Osteoporosis*		
(Other non-prespecified comorbidities….)		

All comorbidities measured by Self-Administered Comorbidity Questionnaire

Example figure presenting clinical course, from van der Gaag et al (3):



Proportion of number of comorbidities among patients at baseline, example from Rundell et al (29):

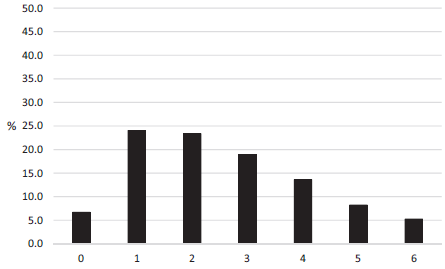


Figure 1. Proportion for number of additional pain sites among those with persistent back pain.

RMDQ middle value presented at each time point, presented based on number of comorbidities (29):

Table: Unadjusted RMDQ score at each timepoint in total cohort and by number of comorbidities

	Baseline	**3 months**	**6 months**	**12 months**
Total cohort	Xx	Xx	Xx	xx
No. of comorbidities				
0	Xx	Xx	Xx	xx
1				
2				
3				
4				
5				
6				

RMDQ = Roland-Morris Disability Questionnaire

Association between comorbidities and disability during 1-year follow-up:

Table: Estimates from **mixed model(XX)** of effect of comorbidities on RMDQ score during 1 year of follow-up

	β	**95% CI**	**R^2**
Comorbidities~			
Covariates			
Comorbidities w/covariates*			

RMDQ = Roland-Morris Disability Questionnaire
~unadjusted effect estimate
*adjusted for time, age, gender, education level, smoking status, hazardous alcohol consumption, back pain duration, probable radicular leg pain, (recruitment profession?)
^adjusted for age, gender, education level, smoking status, hazardous alcohol consumption, back pain duration, probable radicular leg pain, (recruitment profession?)

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